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(54) Title: PRODUCT FOR TREATING GYNECOMASTIA

(57) Abstract: The invention provides a method of treating gynecomastia in a patient being treated with an antiandrogen, which method comprises administering to a patient in need thereof a therapeutically effective amount of an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, or a pharmaceutical composition comprising a said aromatase inhibitor. The use of a said aromatase inhibitor in the preparation of a pharmaceutical composition for treating gynecomastia induced by antiandrogen therapy and a kit containing the said aromatase inhibitor and an antiandrogen are also provided.

PRODUCT FOR TREATING GYNECOMASTIA

Background

This invention relates to a method of treating gynecomastia in patients being treated with an antiandrogen, who are in need of such treatment. This invention more particularly relates to a method of treating gynecomastia in prostatic cancer and in benign prostatic hypertrophy patients being treated with an antiandrogen, who are in need of such treating, comprising administering to such patients in association with therapeutically effective amounts of the antiandrogen, an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, or pharmaceutical compositions thereof.

Prostatic cancer has been treated with antiandrogens. Benign prostatic hypertrophy, a particularly common problem in older men, has been treated with antiandrogens and by use of estrogenic substances. The use of estrogenic substances has undesirable, life-threatening side effects due to the inherent properties of the estrogenic substances.

The use of antiandrogens, e.g. bicalutamide, flutamide, nilutamide and cyproterone acetate, while devoid of life-threatening side effects associated with treatment with estrogenic substances, produces gynecomastia in up to 40% of non-castrated males studied, including normal subjects and advanced prostate cancer patients. Gynecomastia interferes with continued patient compliance with the antiandrogen therapy.

Accordingly, there is a need in therapy for a method of treating gynecomastia in patients being treated with an antiandrogen, e.g. bicalutamide, flutamide, nilutamide and cyproterone acetate, who are in need of such treatment.

Summary of the invention

The invention provides a method of treating gynecomastia in patients being treated with an antiandrogen in need of such treating, which comprises administering to such patients a therapeutically effective amount of an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, or a pharmaceutical composition thereof.

Detailed description of the invention

In one preferred aspect, the present invention provides an effective method of treating

gynecomastia in patients, being treated with an antiandrogen to treat androgen-dependent or androgen-caused disease states, which patients are in need of such treating, by administering therapeutically effective amounts of the antiandrogen in association with an aromatase inhibitor selected from exemestane, anastrozole, letrozole and fadrozole, or pharmaceutical compositions thereof.

Examples of such androgen-dependent or androgen-caused disease states are prostatic cancer and benign prostate hypertrophy.

Accordingly, in another aspect, the present invention provides a method of treating gynecomastia in prostatic cancer or benign prostatic hypertrophy patients in need of such treating, which comprises administering to such patients in association with a therapeutically effective amount of an antiandrogen a therapeutically effective amount of an aromatase inhibitor selected form exemestane, formestane, anastrozole, letrozole and fadrozole or pharmaceutical compositions thereof.
Preferred aromatase inhibitor is exemestane.

In a further aspect, the present invention provides the use of an aromatase inhibitor selected form exemestane, formestane, anastrozole, letrozole and fadrozole in the preparation of a medicament for use in treating gynecomastia in a patient undergoing a simultaneous, separate or sequential treatment with an antiandrogen.

In a further aspect, the present invention provides a kit comprising, in suitable container means, a pharmaceutical composition containing an antiandrogen, for instance as exemplified above, as the active agent, and a pharmaceutical composition containing an aromatase inhibitor selected form exemestane, formestane, anastrozole, letrozole and fadrozole, as the active agent, wherein the aromatase inhibitor is for use in treating gynecomastia in patients, being treated with the antiandrogen.
The antiandrogen and the aromatase inhibitor may be present within a single or distinct container means.
Preferably such kit contains antiandrogen bicalutamide and aromatase inhibitor exemestane.

According to the method of treatment of the present invention, the active compounds may be administered either together, separately, simultaneously or sequentially, in any order, as discussed hereinafter. Preferably the active compounds are administered

substantially simultaneously.

By the term «patients in need of such treating» is meant «male patients with functioning gonads who are being treated with antiandrogen and who exhibit or are likely to exhibit symptoms of gynecomastia». Male patients with functioning gonads have not been surgically castrated or chemically castrated by chronic administration of a LH-RH agonist or antagonist.

Preferred examples of antiandrogens according to the invention are: bicalutamide, cyproterone acetate, flutamide and nilutamide, in particular bicalutamide.

Androgen antagonist bicalutamide is known e.g. from EP-100172.
Cyproterone acetate and flutamide are known e.g. from Cancer Treat. Res., 94, 231-254, 1998. Nilutamide is known e.g. from The Merck Index, 12th edition, see 6636.
By the term «aromatase inhibitor» is meant a substance that inhibits the aromatic conversion of tesosterone into estradiol. Aromatase inhibitors according to the present invention are fadrozole, letrozole, anastrozole, formestane, and exemestane. Exemestane, letrozole and anastrozole, in particular exemestane, being preferred examples of aromatase inhibitors according to the invention.
Letrozole, fadrozole, anastrozole formestane and exemestane are well known products, see e.g. Cancer. Treat. Res., 94, 231-254,1998.

In this invention, the antiandrogen and the aromatase inhibitor are administered as pharmaceutical compositions via parenteral or oral means. Preferably the antiandrogen and the aromatase inhibitor are administered orally.
The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors.
For instance, the antiandrogen bicalutamide compositions are generally administered in a dosage range of about 10 to 200 mg per day, preferably from about 50 to about 150 mg per day.
The aromatase inhibitor compositions are generally administered in a dosage range of about 0.5 to about 500 mg/daily.
The letrozole compositions are generally administered orally in a dosage from about 0.5 to about 10 mg per day, preferably from about 0.5 to about 2.5 mg per day.
The anastrozole compositions are generally administered orally in a dosage from about

0.5 to about 10 mg per day, preferably from about 1 to about 2 mg per day.

The exemestane compositions are generally administered orally in a dose from about 5 to about 200 mg per day, preferably from about 10 to about 25 mg per day, or parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

The formestane compositions are generally administered parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

In a preferred aspect of this invention, the antiandrogen bicalutamide is administered orally in a daily dose of about 50 mg and the aromatase inhibitor is exemestane, which is administered orally in a daily dose of about 25 mg.

The antiandrogen e.g. bicalutamide and the aromatase inhibitor e.g. exemestane may be compounded into a dosage form suitable for oral or parenteral administration or, provided in the form of a kit as described above.

A tablet or capsule or caplets are particularly convenient forms for oral administration. Such compositions useful in the present invention are typically formulated with conventional pharmaceutical excipients, e.g., spray dried lactose and magnesium stearate into tablets or capsules for oral administration. One or more of the active substances can be worked into tablets or dragee cores by being mixed with solid, pulverulent carrier substances, such as sodium citrate, calcium carbonate or dicalcium phosphate, and binders such as polyvinyl pyrrolidone, gelatin or cellulose derivatives, possibly by adding also lubricants such as magnesium stearate, sodium lauryl sulfate, «Carbowax» or polyethylene glycols. Of course, taste improving substances can be added in the case of oral administration forms.

As further forms of administration, one can use plug capsules, e.g. hard gelatin, as well as closed soft gelatin capsules comprising a softner or plasticizer, e.g. glycerine. The plug capsules contain the active substance preferably in the form of a granulate, e.g., in mixtures with fillers, such as lactose, saccharose, mannitol, starches such as potato starch or amylopectin, cellulose derivatives or highly-dispersed silicic acids. In soft-gelatin capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as vegetable oils or liquid polyethylene glycols.

In place of oral administration, the active compounds may be administered parenterally. In such case, one can use a dispersion of the active substance, e.g., in sesame oil or olive oil.

Following the above treatment and using the described regimen, gynecomastia is inhibited, and in some cases completely prevented.

Claims

What is claimed is:

1. Use of an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole in the preparation of a medicament for use in treating gynecomastia in a patient undergoing a simultaneous, separate or sequential treatment with an antiandrogen.

2. Use according to claim 1, wherein the aromatase inhibitor is exemestane.

3. Use according to claim 1, wherein the antiandrogen is bicalutamide.

4. Use according to claim 1, wherein the patient is undergoing a simultaneous treatment with the antiandrogen.

5. A method of treating gynecomastia in a patient being treated with an antiandrogen, which method comprises administering to a patient in need thereof a therapeutically effective amount of an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, or a pharmaceutical composition comprising a said aromatase inhibitor.

6. The method of claim 5 wherein the patient is suffering from prostatic cancer or benign prostatic hypertrophy.

7. The method of claim 5 wherein the aromatase inhibitor is exemestane.

8. The method of claim 5 wherein the antiandrogen is selected from bicalutamide, cyproterone acetate, flutamide and nilutamide.

9. The method of claim 5 wherein the antiandrogen is bicalutamide.

10. The method of claim 5 wherein the antiandrogen and the aromatase inhibitor are administered simultaneously.

11. The method of claim 5 wherein the antiandrogen bicalutamide is administered in a

daily dosage of 50 mg and the aromatase inhibitor exemestane is administered in a daily dosage of 25 mg.

12. A kit comprising, in suitable container means, a pharmaceutical composition containing, as an active agent, an antiandrogen and a pharmaceutical composition and containing, as an active agent, an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, wherein the aromatase inhibitor is for use in treating gynecomastia induced by the antiandrogen.

13. A kit according to claim 12, wherein the aromatase inhibitor and the antiandrogen are present in distinct container means.

14. A kit according to claim 12, wherein the antiandrogen is bicalutamide and the aromatase inhibitor is exemestane.

15. A product containing an antiandrogen and an aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole, for separate simultaneous or sequential use in the treatment of gynecomastia induced by the antiandrogen.

INTERNATIONAL SEARCH REPORT

Int. ..ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5685 A61K31/4196 A61K31/167 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	COOMBES R C ET AL: "AROMATASE INHIBITORS AND THEIR USE IN THE SEQUENTIAL SETTING" ENDROCRINE-RELATED CANCER,JOURNAL OF ENDOCRINOLOGY LTD., BRISTOL,GB, vol. 6, no. 2, June 1999 (1999-06), pages 259-263, XP000986876 ISSN: 1351-0088 the whole document	1-15
Y	GB 2 102 287 A (SCHERING AG) 2 February 1983 (1983-02-02) claims 1-87	12-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Int. ational Application No
PCT/EP 00/12533

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HABENICHT U -F ET AL: "SELECTIVE INHIBITION OF ANDROSTENEDIONE-INDUCED PROSTATE GROWTH IN INTACT BEAGLE DOGS BY A COMBINED TREATMENT WITH THE ANTIANDROGEN CYPROTERONE ACETATE AND THE AROMATASE INHIBITOR 1-METHYL-ANDROSTA-1,4-DIENE-3,17-DIONE (1-METHYL-ADD)" PROSTATE,US,WILEY-LISS, NEW YORK, NY, vol. 14, no. 4, 1989, pages 309-322, XP000874661 ISSN: 0270-4137 abstract	1-15
A	HABENICHT U -F ET AL: "SYNERGIC INHIBITORY EFFECTS OF THE AROMATASE INHIBITOR 1-METHYL- ANDROSTA-1, 4-DIENE-3, 17-DIONE AND THE ANTIANDROGEN CYPROTERONE ACETATE ON ANDROSTENEDIONE-INDUCED HYPERPLASTIC EFFECTS IN THE PROSTATES OF CASTRATED DOGS" PROSTATE,US,WILEY-LISS, NEW YORK, NY, vol. 11, no. 2, 1987, pages 133-143, XP000874660 ISSN: 0270-4137 abstract	1-15

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